Comparison of two novel agents in slowing the progression of chronic kidney disease in patients with type 2 diabetes

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Abstract

Chronic kidney disease (CKD) is a progressive disease process that leads to a decline in kidney function and eventual kidney failure. One of the leading causes of CKD is type 2 diabetes. Novel diabetic agents have been developed and have shown promise in slowing the progression of CKD in patients with type 2 diabetes. The purpose of this review was to compare SGLT-2 inhibitors (I) and GLP-1 receptor agonists (C) to determine their impact on nephropathy indicators (O) in type 2 diabetic patients with CKD (P).

Introduction

- Chronic kidney disease (CKD) is a progressive disease process leading to kidney function decline and failure
- One of the leading causes of CKD is type 2 diabetes[1]
- 9.4% of the U.S. population (30.3 million people) have diabetes with type 2 accounting for 90-95% of cases[2]
- Approximately 35-40% of patients with type 2 diabetes have some degree of kidney disease[3,4]
- Novel agents have been developed to help manage patients with type 2 diabetes with hopes of renoprotective benefits
- These agents include sodium-glucose cotransporter-2 inhibitors (SGLT-2) and glucagon-like peptide-1 (GLP-1) receptor agonists

Methods

- A literature search was conducted in November 2018
- Pub Med:
  - (nephropathy[Title/Abstract]) AND sglt2 inhibitor[Title/Abstract]
  - "nephropathy AND glp-1 receptor agonist"
  - Human studies published in the last 10 years written in English
- Biomedical Sciences Reference Collection:
  - "nephropathy (as a subject term) AND sglt2 inhibitors NOT mice or rats or rodents"
  - "nephropathy (as a subject term) AND glp1 receptor agonists NOT mice or rats or rodents"
  - Written in English since 2013, scholarly peer reviewed journals, and full texts
- Inclusion of at least one marker of nephropathy: proteinuria, creatinine clearance, estimated glomerular filtration rate
- 8 articles were critically appraised and compared

Results

- Imamura et al and Dicembrini et al showed risk reduction of developing nephropathy, slower decline in eGFR, and decrease in proteinuria in patients receiving GLP-1 receptor agonists
- Four of 6 studies on SGLT-2 inhibitors found that patients treated with SGLT-2 inhibitors either experienced an increase, no change, or slower decrease in eGFR compared to the control group
- Heerspink et al and Kohan et al showed that eGFR initially declined in patients taking SLGT-2 inhibitors but stabilized by 2 years to a rate slower than that of the comparison group
- Wanner et al showed a 39% decrease in risk of development of nephropathy in the group treated with the SGLT-2 inhibitor empagliflozin

Table 1. Comparison of Results

Study	Change in eGFR (mL/min/ 1.73m²)	Serum Creatinine	BUN	Urine Albumin: Creatinine Ratio	Creatinine Clearance (mL/min)	Incidence of Nephropathy (defined by various measures)
Dicembrini et al (2017)	n/a	n/a	n/a	n/a	n/a	S G
Heerspink et al (2017)	S G	n/a	n/a	S G	n/a	n/a
Imamura et al (2013)	S G	n/a	n/a	S G	n/a	n/a
Kohan et al (2014)	NS G	NS G	n/a	NS G	NS B	n/a
Perkovic et al (2019)	NS G	S G	n/a	n/a	n/a	S G
Wanner et al (2016)	S G	S G	n/a	S G	n/a	S G
Yale et al (2014)	NS B	NS B	NS B	NS G	n/a	n/a
Yamout et al (2014)	NS B	n/a	n/a	n/a	n/a	S G

Key: S = significant based on p value (p<0.01); NS = not significant (no p value or p value not significant)

eGFR	Serum Creatinine	BUN	Urine Albumin:Creatinine Ratio	Creatinine Clearance
G = increase, no change, or slower decrease in eGFR in treatment group relative to control	G = decrease, no change, or slower increase in serum creatinine in treatment group relative to control	G = decrease, no change, or slower increase in BUN in treatment group relative to control	G = decrease, no change, or slower increase in ACR in treatment group relative to control	G = increase, no change, or slower decrease in treatment group relative to control
B = larger decrease in eGFR after treatment relative to control	B = larger increase in serum creatinine after treatment relative to control	B = larger increase in BUN after treatment relative to control	B = larger increase in ACR after treatment relative to control	B = larger decrease after treatment relative to control

Discussion

Traditionally, patients with type 2 diabetes are treated with metformin, insulin, as well as ACEIs or ARBs, to provide glycemic control and renoprotection. However, once patients have progressed to CKD, this treatment regimen is not as successful at slowing this process. Slowing the progression of CKD can delay the decline in eGFR and the need to start dialysis in this patient population. The data gathered in this review suggests that, in the long term, SLGT-2 inhibitors might be beneficial for stabilizing eGFR and preventing rapid decline. Data from the multiple studies that lasted at least 2 years showed that, initially, patients treated with SGLT-2 inhibitors experience a brief sharp decline in eGFR, which then trends back towards baseline and stabilizes over time. One of the explanations offered was that the initial volume depletion associated with SGLT-2 inhibitors created a dose-dependent effect that initially shows a decrease in eGFR and increase in other renal markers such as BUN and serum creatinine. Additionally, there exists research indicating SGLT-2 inhibitors have other beneficial impacts on health outcomes, such as improving glycemic control, lowering systolic blood pressure, and reducing body weight. The two studies evaluating GLP-1 agonists suggest they might have a role in decreasing proteinuria, rate of eGFR decline, and risk of nephropathy.

Conclusion

There is limited generalizability of the results of the SGLT-2 clinical trials, as the majority required patients to have an eGFR of at least 30 mL/min/1.73m^2 and there was limited racial diversity among the samples. The initial data from these clinical trials are promising, and further studies should be conducted that increase length of treatment and diversify the treatment group. There exists no direct comparison between SGLT-2 inhibitors and GLP-1 receptor agonists, so a definitive comparison cannot be made. As there exists limited treatment options that can assist in slowing the progression of CKD, SGLT-2 inhibitors should be seriously considered given the preliminary renoprotective effects they exhibit, limited relative safety concerns, and evidence for improved glycemic control, systolic blood pressure, and body weight.

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